

(b) a polypeptide comprising a purified human Asp2(b) amino acid sequence set forth in SEQ ID NO: 6 or a fragment thereof that cleaves APP;

(c) a polypeptide comprising the murine Asp2 amino acid sequence set forth in SEQ ID NO: 8, or a fragment thereof that cleaves APP;

(d) a polypeptide comprising a purified polypeptide having an amino acid sequence that is at least 95% identical to (a), (b), or (c).

153. A purified polypeptide according to claim 151, comprising a purified human Asp2(a) amino acid sequence set forth in SEQ ID NO: 4 or a fragment thereof that cleaves APP.

154. A purified polypeptide according to claim 151, said polypeptide comprising a portion of the human Asp2(a) amino acid sequence set forth in SEQ ID NO: 4, said portion including amino acids 22-501 of SEQ ID NO: 4 and lacking amino acids 1-21.

155. A polypeptide according to claim 154, beginning with the N-terminal sequence ETDEEP.

156. A purified polypeptide according to claim 151, said polypeptide comprising a portion of the human Asp2(a) amino acid sequence set forth in SEQ ID NO: 4 effective to cleave APP, said polypeptide lacking transmembrane domain amino acid residues 455-477 of SEQ ID NO: 4.

157. A polypeptide according to claim 155, said polypeptide lacking amino acids 454-501 of SEQ ID NO: 4.

158. A purified polypeptide according to claim 151, comprising a purified human Asp2(b) amino acid sequence set forth in SEQ ID NO: 6 or a fragment thereof that cleaves APP.

159. A purified polypeptide according to claim 151, said polypeptide comprising a portion of the human Asp2(b) amino acid sequence set forth in SEQ ID NO: 6, said portion including amino acids 22-476 of SEQ ID NO: 6 and lacking amino acids 1-21.

160. A purified polypeptide according to claim 151, said polypeptide comprising a portion of the human Asp2(b) amino acid sequence set forth in SEQ ID NO: 6 effective to cleave APP, said polypeptide lacking transmembrane domain amino acid residues 430-452 of SEQ ID NO: 6.

161. A purified polypeptide according to claim 151, comprising the murine Asp2 amino acid sequence set forth in SEQ ID NO: 8, or a fragment thereof that cleaves APP.

162. A purified polypeptide according to claim 151 comprising a fragment of a mammalian Asp2 polypeptide, wherein the purified polypeptide lacks the transmembrane domain of said mammalian Asp2 polypeptide.

163. A fusion protein comprising a polypeptide of claim 151, and which further includes a heterologous tag amino acid sequence.

164. A polypeptide of claim 151, wherein the polypeptide cleaves human APP or human APP-Sw at the β -secretase recognition site.

165. A polypeptide of claim 151, wherein the polypeptide lacks any mammalian Asp2 pro-peptide sequence.

166. A polypeptide according to claim 151, selected from the group consisting of:

(a) a polypeptide comprising a portion of the amino acid sequence set forth in SEQ ID NO: 4 effective to cleave APP, wherein the polypeptide lacks amino acids 1-45 of SEQ ID NO: 4; and

(b) a polypeptide comprising a portion of the amino acid sequence set forth in SEQ ID NO: 6 effective to cleave APP, wherein the polypeptide lacks amino acids 1-45 of SEQ ID NO: 6.

167. A purified polynucleotide comprising a nucleotide sequence that encodes a polypeptide of claim 151.

168. A polynucleotide according to claim 167, selected from the group consisting of:

- (a) a polynucleotide comprising the nucleotide sequence set forth in SEQ ID NO: 3;
- (b) a polynucleotide comprising the nucleotide sequence set forth in SEQ ID NO: 5;
- (c) a polynucleotide comprising the nucleotide sequence set forth in SEQ ID NO: 7;
- (d) a polynucleotide comprising a nucleotide sequence that is at least 95% identical to (a), (b), or (c), and that encodes a polypeptide that cleaves APP; and
- (e) a fragment of (a), (b), (c), or (d) that encodes a polypeptide that cleaves APP.

169. A polynucleotide according to claim 167 comprising a nucleotide sequence selected from the group consisting of SEQ ID NOS: 21, 23, 25, 27, 29, and 31.

170. A purified polynucleotide according to claim 167, selected from the group consisting of:

- (a) a purified polynucleotide that comprises a nucleotide sequence that encodes amino acids 22-501 of SEQ ID NO: 4 and lacks adjacent nucleotide sequence encoding amino acids 1-21 of SEQ ID NO: 4; and
- (b) a purified polynucleotide that comprises a nucleotide sequence that encodes amino acids 22-476 of SEQ ID NO: 6 and lacks adjacent nucleotide sequence encoding amino acids 1-21 of SEQ ID NO: 6.

171. A purified polynucleotide according to claim 167, selected from the group consisting of:

(a) a purified polynucleotide comprising a nucleotide sequence that encodes a portion of the human Asp2(a) amino acid sequence set forth in SEQ ID NO: 4 effective to cleave APP, and wherein the polynucleotide lacks adjacent nucleotide sequence encoding transmembrane domain amino acid residues 455-477 of SEQ ID NO: 4; and

(b) a purified polynucleotide comprising a nucleotide sequence that encodes a portion of the human Asp2(a) amino acid sequence set forth in SEQ ID NO: 6 effective to cleave APP, and wherein the polynucleotide lacks adjacent nucleotide sequence encoding transmembrane domain amino acid residues 430-452 of SEQ ID NO: 6.

172. A purified polynucleotide according to claim 171, said polynucleotide lacking nucleotide sequence encoding amino acids 454-501 of SEQ ID NO: 4.

173. A purified polynucleotide according to claim 167 comprising a fragment of a mammalian Asp2 polynucleotide, wherein the fragment lacks nucleotide sequence encoding the transmembrane domain of said mammalian Asp2 polypeptide.

174. A purified polynucleotide according to claim 167, wherein the polynucleotide lacks a nucleotide sequence encoding a mammalian Asp2 pro-peptide sequence.

175. A vector comprising a polynucleotide according to claim 167.

176. A vector according to claim 175 that is an expression vector wherein the polynucleotide is operably linked to an expression control sequence.

177. A host cell transformed or transfected with a polynucleotide according to claim 167.

178. A host cell transformed or transfected with a vector according to claim 176.

179. A host cell according to claim 178 that is a mammalian cell.

180. A host cell according to claim 178 that expresses the polypeptide on its surface.

181. A host cell according to claim 178 that secretes the polypeptide encoded by the polynucleotide, wherein the secreted polypeptide lacks a transmembrane domain.

182. A host cell according to claim 177, wherein the host cell is transfected with a nucleic acid comprising a nucleotide sequence that encodes an amyloid precursor protein (APP) or fragment thereof that includes a protease recognition site recognized by the polypeptide.

183. A host cell according to claim 182, wherein the host cell is transfected with a nucleic acid comprising a nucleotide sequence that encodes an amyloid precursor protein (APP).

184. A host cell according to claim 183, wherein the host cell is transfected with a nucleic acid comprising a nucleotide sequence that encodes an amyloid precursor protein (APP) that includes two carboxy-terminal lysine residues.

185. A host cell according to claim 182, wherein the APP or fragment thereof includes the APP Swedish mutation sequence KM → NL immediately upstream of the β-secretase cleavage site.

186. A host cell according to claim 182 that expresses the polypeptide and the APP or APP fragment on its surface.

187. A method of making a polypeptide that cleaves APP, comprising steps of culturing a host cell according to claim 177 in a culture medium under conditions in which the cell produces the polypeptide that is encoded by the polynucleotide.

188. A method according to claim 187, further comprising a step of purifying the polypeptide from the cell or the culture medium.

189. A method for identifying agents that inhibit the activity of human Asp2 aspartyl protease (Hu-Asp2), comprising the steps of:

- (a) contacting amyloid precursor protein (APP) and a polypeptide according to claim 151 in the presence and absence of a test agent;
- (b) determining the APP processing activity of the polypeptide in the presence and absence of the test agent; and
- (c) comparing the APP processing activity of the polypeptide in the presence of the test agent to the activity in the absence of the test agent to identify an agent that inhibits the APP processing activity of the polypeptide, wherein reduced activity in the presence of the test agent identifies an agent that inhibits Hu-Asp2 activity.

190. A method according to claim 189, wherein the polypeptide is a recombinant polypeptide purified and isolated from a cell transformed or transfected with a polynucleotide comprising a nucleotide sequence that encodes the polypeptide.

191. A method according to claim 189,
wherein the polypeptide is expressed in a cell transformed or transfected with a polynucleotide comprising a nucleotide sequence that encodes the polypeptide,
wherein the contacting comprises growing the cell in the presence and absence of the test agent, and
wherein the determining step comprises measuring APP processing activity of the cell.

192. A method according to claim 189, wherein the determining step comprises measuring the production of amyloid beta peptide by the cell in the presence and absence of the test agent.

193. A method according to claim 191 or 192, wherein the cell is a human embryonic kidney cell line 293 (HEK293) cell.

194. A method according to claim 190 wherein the nucleotide sequence is selected from the group consisting of:

(a) a nucleotide sequence encoding the Hu-Asp2(a) amino acid sequence set forth in SEQ ID NO: 4;

(b) a nucleotide sequence encoding the Hu-Asp2(b) amino acid sequence set forth in SEQ ID NO: 6;

(c) a nucleotide sequence encoding a fragment of Hu-Asp2(a) (SEQ ID NO: 4) or Hu-Asp2(b) (SEQ ID NO: 6), wherein said fragment exhibits aspartyl protease activity characteristic of Hu-Asp2(a) or Hu-Asp2(b); and

(d) a nucleotide sequence of a polynucleotide that hybridizes under stringent hybridization conditions to a Hu-Asp2-encoding polynucleotide selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 5.

195. A method according claim 190, wherein the Hu-Asp2 comprises the Hu-Asp2(a) amino acid sequence set forth in SEQ ID NO: 4.

196. A method according to claim 190, wherein the Hu-Asp2 comprises the Hu-Asp2(b) amino acid sequence set forth in SEQ ID NO: 6.

197. A method according to claim 190, wherein the Hu-Asp2 comprises a fragment of Hu-Asp2(a) (SEQ ID NO: 4) or Hu-Asp2(b) (SEQ ID NO: 6), wherein said fragment exhibits aspartyl protease activity characteristic of Hu-Asp2(a) or Hu-Asp2(b).

198. A method according to claim 190, wherein the cell comprises a vector that comprises the polynucleotide.

199. A method according to claim 189, wherein the APP comprises the Swedish mutation (K→N, M→L) adjacent to the β -secretase processing site.

200. A method according to claim 189, wherein the APP further comprises a carboxy-terminal di-lysine.

201. A method for identifying agents that modulate the activity of Asp2 aspartyl protease, comprising the steps of:

- Asp2
- (a) contacting a purified and isolated polypeptide according to claim 151 and amyloid precursor protein (APP) in the presence and absence of a test agent, wherein the Asp2 aspartyl protease is encoded by a nucleic acid molecule that hybridizes under stringent hybridization conditions to a Hu-Asp2-encoding polynucleotide selected from the group consisting of SEQ ID NO: 4 and SEQ ID NO: 6;
 - (b) determining the APP processing activity of the polypeptide in the presence and absence of the test agent; and
 - (c) comparing the APP processing activity of the polypeptide in the presence of the test agent to the activity in the absence of the agent to identify agents that modulate the activity of the polypeptide, wherein a modulator that is an Asp2 inhibitor reduces APP processing and a modulator that is an Asp2 agonist increases such processing.

202. A method according to claim 189, further comprising a step of treating Alzheimer's Disease with an agent identified as an inhibitor of Hu-Asp2 according to steps (a)-(c).

203. A method according to claim 189, further comprising a step of manufacturing a medicament for the treatment of Alzheimer's Disease with an inhibitor identified according to steps (a)-(c).

204. A method for assaying for modulators of β -secretase activity, comprising the steps of:

- (a) contacting a first composition with a second composition both in the presence and in the absence of a putative modulator compound, wherein the first composition comprises a polypeptide according to claim 151, and wherein the second composition comprises a substrate polypeptide having an amino acid sequence comprising a β -secretase cleavage site;
- (b) measuring cleavage of the substrate polypeptide in the presence and in the absence of the putative modulator compound; and
- (c) identifying modulators of β -secretase activity from a difference in cleavage in the presence versus in the absence of the putative modulator compound, wherein a modulator that is a β -secretase antagonist reduces such cleavage and a modulator that is a β -secretase agonist increases such cleavage.

205. A method according to claim 204, wherein the polypeptide of the first composition comprises a polypeptide purified and isolated from a cell transformed or transfected with a polynucleotide comprising a nucleotide sequence that encodes the polypeptide.

206. A method according to claim 204, wherein the polypeptide of the first composition is expressed in a cell transformed or transfected with a polynucleotide comprising a nucleotide sequence that encodes the polypeptide, and wherein the measuring step comprises measuring APP processing activity of the cell.

207. A method according to claim 204, wherein the first composition comprises a purified human Asp2 polypeptide.

208. A method according to claim 204, wherein the first composition comprises a soluble fragment of a human Asp2 polypeptide that retains Asp2 β -secretase activity.

209. A method according to claim 208 wherein the soluble fragment is a fragment lacking an Asp2 transmembrane domain.

210. A method according to claim 208, wherein the substrate polypeptide of the second composition comprises the amino acid sequence SEVNLDAEFR.

211. A method according to claim 208, wherein the substrate polypeptide of the second composition comprises the amino acid sequence EVKMDAEF.

212. A method according to claim 208, wherein the second composition comprises a polypeptide having an amino acid sequence of a human amyloid precursor protein (APP).

213. A method according to claim 212, wherein the human amyloid precursor protein is selected from the group consisting of: APP695, APP751, and APP770.

214. A method according to claim 213, wherein the human amyloid precursor protein includes at least one mutation selected from a KM-NL Swiss mutation and a V-F London mutation.

215. A method according to claim 212, wherein the polypeptide having an amino acid sequence of a human APP further comprises an amino acid sequence comprising a marker sequence attached amino-terminal to the amino acid sequence of the human amyloid precursor protein.

216. A method according to claim 212, wherein the polypeptide having an amino acid sequence of a human APP further comprises two lysine residues attached to the carboxyl terminus of the amino acid sequence of the human APP.

217. A method according to claim 204, wherein the second composition comprises a eukaryotic cell that expresses amyloid precursor protein (APP) or a fragment thereof containing a β -secretase cleavage site.

218. A method according to claim 217, wherein the APP expressed by the host cell is an APP variant that includes two carboxyl-terminal lysine residues.

219. A method according to claim 204, further comprising a step of treating Alzheimer's Disease with an agent identified as an inhibitor of Hu-Asp2 according to steps (a)-(c).

220. A method according to claim 204, further comprising a step of manufacturing a medicament for the treatment of Alzheimer's Disease with a modulator identified as an antagonist according to steps (a)-(c).

221. A method for identifying agents that inhibit the activity of human Asp2 aspartyl protease (Hu-Asp2), comprising the steps of:

- (a) growing a cell in the presence and absence of a test agent, wherein the cell expresses a polypeptide according to claim 151 and expresses an amyloid precursor protein (APP) that comprises a carboxy-terminal di-lysine (KK);
- (b) determining the APP processing activity of the cell in the presence and absence of the test agent; and
- (c) comparing the APP processing activity in the presence of the test agent to the activity in the absence of the test agent to identify an agent that inhibits the activity of Hu-Asp2, wherein reduced activity in the presence of the test agent identifies an agent that inhibits Hu-Asp2 activity.

222. A method according to claim 221, wherein the APP further comprises the Swedish mutation (K \rightarrow N, M \rightarrow L) adjacent to the β -secretase processing site.

223. A method according to claim 221 or 222, wherein the host cell has been transformed or transfected with a polynucleotide comprising a nucleotide sequence that encodes a Hu-Asp2, wherein said nucleotide sequence is selected from the group consisting of:

- (a) a nucleotide sequence encoding the Hu-Asp2(a) amino acid sequence set forth in SEQ ID NO: 4;
- (b) a nucleotide sequence encoding the Hu-Asp2(b) amino acid sequence set forth in SEQ ID NO: 6;
- (c) a nucleotide sequence encoding a fragment of Hu-Asp2(a) (SEQ ID NO: 4) or Hu-Asp2(b) (SEQ ID NO: 6), wherein said fragment exhibits aspartyl protease activity characteristic of Hu-Asp2(a) or Hu-Asp2(b); and
- (d) a nucleotide sequence of a polynucleotide that hybridizes under stringent hybridization conditions to a Hu-Asp2-encoding polynucleotide selected from the group consisting of SEQ ID NO: 3 and SEQ ID NO: 5.

224. A method according to claim 223, further comprising a step of treating Alzheimer's Disease with an agent identified as an inhibitor of Hu-Asp2 according to steps (a)-(c).

225. A method according to claim 221, further comprising a step of making a medicament for the treatment of Alzheimer's Disease with a test agent identified as an inhibitor according to steps (a)-(c).

226. A method of reducing cellular production of amyloid beta ($A\beta$) from amyloid precursor protein (APP), comprising step of transforming or transfecting cells with an anti-sense reagent capable of reducing Asp2 polypeptide production by reducing Asp2 transcription or translation in the cells, wherein reduced Asp2 polypeptide production in the cells correlates with reduced cellular processing of APP into $A\beta$.

227. A method of reducing cellular production of amyloid beta ($A\beta$) from amyloid precursor protein (APP), comprising steps of:

- (a) identifying mammalian cells that produce $A\beta$; and
- (b) transforming or transfecting the cells with an anti-sense reagent capable of reducing Asp2 polypeptide production by reducing Asp2 transcription or translation in the cells, wherein reduced Asp2 polypeptide production in the cells correlates with reduced cellular processing of APP into $A\beta$.

228. A method according to claim 227, wherein the identifying step comprises diagnosing Alzheimer's disease, where Alzheimer's disease correlates with the existence of cells that produce $A\beta$ that forms amyloid plaques in the brain.

229. A method according to claim 226, wherein the cell is a neural cell.

230. A method according to claim 226, wherein the anti-sense reagent comprises an oligonucleotide comprising a single stranded nucleic acid sequence capable of binding to a Hu-Asp mRNA.

231. A method according to claim 226, wherein the anti-sense reagent comprises an oligonucleotide comprising a single stranded nucleic acid sequence capable of binding to a Hu-Asp DNA.

232. A polypeptide comprising the amino acid sequence of a mammalian amyloid protein precursor (APP) or fragment thereof containing an APP cleavage site recognizable by a mammalian β -secretase, and further comprising two lysine residues at the carboxyl terminus of the amino acid sequence of the mammalian APP or APP fragment.

233. A polypeptide according to claim 232 comprising the amino acid sequence of a mammalian amyloid protein precursor (APP), and further comprising two lysine residues at the carboxyl terminus of the amino acid sequence of the mammalian amyloid protein precursor.

234. A polypeptide according to claim 232, wherein the mammalian APP is a human APP.

235. A polypeptide according to claim 232, wherein the human APP comprises at least one variation selected from the group consisting of a Swedish KM-NL mutation and a London V717-F mutation.

236. A polynucleotide comprising a nucleotide sequence that encodes a polypeptide according to claim 232.

237. A vector comprising a polynucleotide according to claim 236.

238. A vector according to claim 237 wherein said polynucleotide is operably linked to a promoter to promote expression of the polypeptide encoded by the polynucleotide in a host cell.

239. A host cell transformed or transfected with a polynucleotide according to claim 86 or a vector according to claim 237.

240. A host cell according to claim 239 that is a mammalian cell.

241. An isolated nucleic acid molecule comprising a nucleotide sequence at least 95% identical to a sequence selected from the group consisting of:

(a) a nucleotide sequence encoding a Hu-Asp polypeptide selected from the group consisting of Hu-Asp1, Hu-Asp2(a), and Hu-Asp2(b), wherein said Hu-Asp1, Hu-Asp2(a) and Hu-Asp2(b) polypeptides have the complete amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, and SEQ ID No:6, respectively; and

(b) a nucleotide sequence complementary to the nucleotide sequence of (a).

242. The nucleic acid molecule of claim 241, wherein said Hu-Asp polypeptide is Hu-Asp1.

243. The nucleic acid molecule of claim 241, wherein said Hu-Asp polypeptide is Hu-Asp2(a).

244. The nucleic acid molecule of claim 241, wherein said Hu-Asp polypeptide is Hu-Asp2(b).

245. An isolated nucleic acid molecule comprising polynucleotide which hybridizes under stringent conditions to a polynucleotide comprising a nucleotide sequence selected from:

(a) a nucleotide sequence encoding a Hu-Asp polypeptide selected from the group consisting of Hu-Asp1, Hu-Asp2(a), and Hu-Asp2(b), wherein said Hu-Asp1, Hu-Asp2(a) and Hu-Asp2(b) polypeptides have the complete amino acid sequence of SEQ ID NO:2, SEQ ID NO:4, and SEQ ID No:6, respectively; and

(b) a nucleotide sequence complementary to the nucleotide sequence of (a).

246. A vector comprising the nucleic acid molecule of claim 241.

247. The vector of claim 246, wherein said nucleic acid molecule is operably linked to a promoter for the expression of a Hu-Asp polypeptide.

248. A host cell comprising the vector of claim 247.

249. A method of obtaining a Hu-Asp polypeptide comprising culturing the host cell of claim 248 and isolating said Hu-Asp polypeptide.

250. An isolated Hu-Asp1 polypeptide comprising an amino acid sequence at least 95% identical to a sequence comprising the amino acid sequence of SEQ ID NO:2.

251. An isolated Hu-Asp2(a) polypeptide comprising an amino acid sequence at least 95% identical to a sequence comprising the amino acid sequence of SEQ ID NO:4.

252. An isolated Hu-Asp2(a) polypeptide comprising an amino acid sequence at least 95% identical to a sequence comprising the amino acid sequence of SEQ ID NO:8.

253. An isolated antibody that binds specifically to the Hu-Asp polypeptide of any of claims 250-252.

254. A cell according to claim 248 that is a bacterial cell.

255. A bacterial cell of claim 254 where the bacteria is *E. coli*.

256. A cell according to claim 248 that is a eukaryotic cell.

257. A cell according to any one of claims 248 that is an insect cell.

258. An insect cell of claim 257 where the insect is sf9, or High 5.

259. An insect cell of claim 257 where the insect cell is High 5.
260. A cell according to claim 248 that is a mammalian cell.
261. A mammalian cell of claim 260 selected from the group consisting of human, rodent, lagomorph, and primate cells.
262. A mammalian cell of claim 261 that is a human cell.
263. A mammalian cell of claim 262 selected from the group consisting of HEK293 and IMR-32 cells.
264. A mammalian cell of claim 261 that is a primate cell.
265. A primate cell of claim 264 that is a COS-7 cell.
266. A mammalian cell of claim 261 that is a rodent cell.
267. A rodent cell of claim 266 selected from, CHO-K1, Neuro-2A, 3T3 cells.
268. A cell according to claim 248 that is a yeast cell.
269. A cell according to claim 248 that is an avian cell.
270. Any isoform of Amyloid Precursor Protein (APP) modified such that the last two carboxy terminus amino acids of that isoform are both lysine residues.
271. The isoform of APP from claim 270 comprising the isoform known as APP695 modified so that its last two carboxy terminus amino acids are lysines.

272. The isoform of claim 271 comprising SEQ ID: 16.

273. The isoform variant of claim 271 comprising SEQ ID NO: 18 or 20.

274. A nucleic acid encoding a polypeptide according to claim 270.

275. An eukaryotic cell comprising a nucleic acids of claim 274.

276. An eukaryotic cell comprising a polypeptide of claim 270.

277. An eukaryotic cell according to claim 275 that is a mammalian cell.

278. A mammalian cell according to claim 277, selected from the group consisting of HEK293 and Neuro2a.

279. A method according to claim 187 in which the determining or measuring step comprises measuring the amount of amyloid beta-peptide released into growth medium of the cell and/or the amount of CTF99 fragments of APP in cell lysates.

280. The method of claim 279 wherein the cell is from a human, rodent or insect cell line.

281. A method for identifying agents that modulate the activity of human Asp1 aspartyl protease (Hu-Asp1), comprising the steps of:

- (a) contacting amyloid precursor protein (APP) and a Hu-Asp1 polypeptide in the presence and absence of the test agent;
- (b) determining the APP processing activity of the polypeptide in the presence and absence of the test agent; and
- (c) comparing the APP processing activity of the polypeptide in the presence of the test agent to the activity in the absence of the test agent to identify an agent that modulates

the APP processing activity of the polypeptide, wherein a modulator that is an Asp1 inhibitor reduces such cleavage and a modulator that is a Asp1 agonist increases such cleavage.

282. A method according to claim 281 wherein the polypeptide comprises an amino acid sequence at least 95% identical to a sequence comprising the amino acid sequence of SEQ ID NO: 2.

283. A method according to claim 281, wherein the polypeptide is a recombinant polypeptide purified and isolated from a cell transformed or transfected with a polynucleotide comprising a nucleotide sequence that encodes the polypeptide.

284. A method according to claim 281, wherein the polypeptide is expressed in a cell transformed or transfected with a polynucleotide comprising a nucleotide sequence that encodes the polypeptide, wherein the contacting comprises growing the cell in the presence and absence of the test agent, and wherein the determining step comprises measuring APP processing activity of the cell.

285. A method according to claim 284, wherein the determining step comprises measuring the production of amyloid beta peptide by the cell in the presence and absence of the test agent.

286. A method according to claim 284, wherein the cell is a human embryonic kidney cell line 293 (HEK293) cell.

287. A method according to claim 283 wherein the nucleotide sequence is selected from the group consisting of

(a) a nucleotide sequence encoding the Hu-Asp1 amino acid sequence set forth in SEQ ID NO: 1;

(b) a nucleotide sequence encoding a fragment of Hu-Asp1 (SEQ ID NO: 1), wherein said fragment exhibits aspartyl protease activity characteristic of Hu-Asp1

(c) a nucleotide sequence of a polynucleotide that hybridizes under stringent hybridization conditions to a Hu-Asp1-encoding polynucleotide having the sequence set forth in SEQ ID NO: 1.

288. A method according to claim 284, wherein the cell comprises a vector that comprises the polynucleotide.

289. A method according to claim 281, wherein the APP comprises the Swedish mutation (K→N, M→L) adjacent to the β -secretase processing site.

290. A method according to claim 281, wherein the APP further comprises a carboxy-terminal di-lysine.

291. A method according to claim 281, wherein the test agent is an inhibitor.

292. A method according to claim 281, wherein the test agent is an agonist.

293. A method according to claim 281, further comprising a step of treating Alzheimer's Disease with an agent identified as an modulator of Hu-Asp1 according to steps (a)-(c).

294. A method according to claim 281, further comprising a step of making a medicament for the treatment of Alzheimer's Disease with a test agent identified as an inhibitor according to steps (a)-(c).

295. A method of reducing cellular production of amyloid beta ($A\beta$) from amyloid precursor protein (APP), comprising step of transforming or transfecting cells with an anti-sense reagent capable of reducing Asp1 polypeptide production by reducing Asp1 transcription or translation in the cells, wherein reduced Asp1 polypeptide production in the cells correlates with reduced cellular processing of APP into $A\beta$.

296. A method of reducing cellular production of amyloid beta (A β) from amyloid precursor protein (APP), comprising steps of:

- (a) identifying mammalian cells that produce A β ; and
- (b) transforming or transfecting the cells with an anti-sense reagent capable of reducing Asp1 polypeptide production by reducing Asp1 transcription or translation in the cells, wherein reduced Asp1 polypeptide production in the cells correlates with reduced cellular processing of APP into A β .

297. A method according to claim 296, wherein the identifying step comprises diagnosing Alzheimer's disease, where Alzheimer's disease correlates with the existence of cells that produce A β that forms amyloid plaques in the brain.

298. A method according to claim 295 or 296, wherein the cell is a neural cell.

299. A method according to any one of claims 298, wherein the anti-sense reagent comprises an oligonucleotide comprising a single stranded nucleic acid sequence capable of binding to a Hu-Asp1 mRNA.

300. A method for the identification of an agent that decreases the activity of a Hu-Asp polypeptide selected from the group consisting of Hu-Asp1, Hu-Asp1(a), and Hu-Asp2(b), the method comprising

- (a) determining the activity of said Hu-Asp polypeptide in the presence of a test agent and in the absence of a test agent; and
- (b) comparing the activity of said Hu-Asp polypeptide determined in the presence of said test agent to the activity of said Hu-Asp polypeptide determined in the absence of said test agent;

whereby a lower level of activity in the presence of said test agent than in the absence of said test agent indicates that said test agent has decreased the activity of said Hu-Asp polypeptide. --